From Pupil to Performance: Exploring the role of tonic norepinephrine levels in response inhibition using pretrial pupil measures

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Abstract

Response inhibition is key to flexible behavior. Importantly, performance in any task, including response inhibition tasks, fluctuates on a moment-to-moment basis. Using pupillometry, we investigated the relationship between these behavioral fluctuations in response inhibition and naturally-occurring fluctuations of norepinephrine (NE) levels in the brain before a given trial has even started. This was motivated by earlier pharmacological work suggesting a pivotal role of NE in response inhibition, in particular. We specifically used two pupillometry proxies for pretrial (tonic) NE levels, the absolute pretrial pupil size and its derivative, and investigated whether and to which degree they were related to response-inhibition performance in a stop-signal task. Specifically, we investigated the relationship to stopping success, and the speed of the go response (GoRT) and that of the stop response (SSRT). In two experiments, we showed that larger pretrial pupil measures predicted (1) lower stopping success, (2) faster GoRTs (particularly so when the go response needed to be executed in a stop context), and some evidence for (3) faster SSRTs. Taken together, our findings show a clear pattern that pretrial pupil measures predict behavioral fluctuations in response inhibition, which suggests that tonic levels of NE are involved in the regulation of these behavioral fluctuations. Yet, our work furthermore indicates that this involvement is not stopping-specific, given its effect on both the go and the stop response.

Key words: response inhibition, pretrial pupil size, proactive control, pupillometry, stop-signal task

1 Introduction

Response inhibition is the ability to cancel or suppress pre-planned or ongoing actions, facilitating adaptive behavior by allowing for the adjustment of behaviour to changing environments or internal goals. It is often considered one of the core executive functions that allows people to have dynamic and goal-directed behaviour (e.g. Miyake & Friedman, 2012; Miyake et al., 2000; but see also Friedman & Miyake, 2017). As such, deficits in response inhibition can have a significant influence on the quality of daily life, with response-inhibition deficits having been suggested to underlie (and to also be important for the successful treatment of) many disorders, most prominently including Attention-Deficit Hyperactivity Disorder (ADHD) but also for example Obsessive-Compulsive Disorder and schizophrenia (see Lipszyc & Schachar, 2010, for a review).

In the lab, a popular task to measure response inhibition is the stop-signal task, in which participants have to do a simple 'go' task unless a stop signal appears after some delay (the so-called 'stop-signal delay', SSD; Logan & Cowan, 1984; Verbruggen et al., 2019). Response inhibition is often conceptualized as a horse race between executing a go response and a stop response (Logan & Cowan, 1984). The stop response races against the go response to cancel it before it is executed; inhibition is successful if the stop response finishes first, and unsuccessful if the go response finishes first instead. Thereby, the success of response inhibition depends on the combination of the SSD (representing the head start the go response gets in the race), the speed of the go response, and the speed of the stop response. Even though the speed of the stop response cannot be directly observed, the horse-race model provides a formal framework to infer this important response-inhibition component, called the stop-signal response time (SSRT; Logan & Cowan, 1984). Importantly, neither the speed of the go response nor that of the stop response are (usually assumed to be) constant, e.g. people are sometimes naturally fast and at other times slow in responding to the go stimulus and/or the stop signal [1]. Here, we will investigate these moment-to-moment behavioral fluctuations of response inhibition.

More specifically, leveraging pupillometry, we will focus on the role of naturally-occurring fluctuations in pupil size before a given trial begins. The relevance of these pretrial measures has been increasingly appreciated in different task domains, with the frequent finding that pretrial pupil measures explain subsequent performance on cognitive tasks (e.g., Gilzenrat et al., 2010; Murphy et al., 2014; Nassar et al., 2012; Tromp et al., 2022; Tsukahara & Engle, 2021; van den Brink et al., 2016; however, see also Martin et al., 2022), and so may as well affect the performance on the stop-signal task by affecting the speed of the go response and/or that of the stop response. Even more importantly, pupil size is believed to be indicative of activity in the norepinephrine (NE) system (Gilzenrat et al., 2010; Rajkowski et al.,

[1] Note that this is reflected in the fact that speed of the go response follows a skewed distribution that is typical of reaction times Hohle, 1965; for the speed of the stop response, the same distribution is assumed in computational models of response inhibition Logan et al., 2014; Matzke et al., 2013; Matzke et al., 2017. Still, also note that early, non-parametric models of the race do assume that the SSRT is constant Logan and Cowan, 1984; Verbruggen et al., 2019).

1994; Reimer et al., 2014), a system that has previously been strongly linked to response inhibition (as we explain below). This study will thereby allow us to further understand the role of the NE system as mechanism driving the behavioral fluctuations in response inhibition.

1.1 The NE system and response inhibition

NE (also known as noradrenaline) is a neuromodulator primarily originating from the locus coeruleus (LC), using its many cortical and subcortical projections. Different aspects of NE levels are referred to as being either tonic (i.e., reflecting the LC baseline activity) or phasic (bursts of LC activity typically in response to an event; Aston-Jones & Cohen, 2005). A number of pharmacological, animal, and neuroimaging studies have shown that NE levels are particularly important for response inhibition, and for SSRT especially (Robbins & Arnsten, 2009). For example, medication like methylphenidate acting on the LC-NE system has been found to normalize inhibition performance in people with ADHD (e.g. Aron et al., 2003; Bedard et al., 2003; Rosch et al., 2016). Even non-stimulant drugs that regulate NE, such as selective NE-reuptake inhibitors including atomoxetine (Chamberlain et al., 2007; Chamberlain et al., 2009), have been found to improve inhibition performance in research on human adults (Chamberlain et al., 2007; Rae et al., 2016; Ye et al., 2022) as well as in animal research using rat and mouse models (Bari et al., 2009; Humby et al., 2013). Also neurophysiological studies have linked the LC to response inhibition; e.g. Liu et al. (2024) used biosensors and pupillometry to couple the LC to inhibitory control during a task where mice had to infrequently inhibit drinking sweet water; while Tomassini et al. (2022) showed that higher LC integrity (i.e., the cell density of the LC) was associated with faster SSRTs, which again suggests a role of the LC in regulating the SSRT specifically. So, across multiple fields, there is converging evidence that NE plays a key role in regulating response inhibition in a potentially rather stopping-specific way.

While it seems likely that pharmacological interventions and variations in the integrity of the LC have relatively strong effects on NE levels, NE levels are also known to naturally fluctuate in ways that may well also be tied to the moment-to-moment fluctuations in behavior (Aston-Jones & Cohen, 2005). One intriguing possibility to investigate this, albeit indirectly, is by means of pupillometry since the LC also has indirect projections to the muscles that dilate and constrict the pupil, and pupil size has been tightly linked to LC-NE activity (Gilzenrat et al., 2010; Rajkowski et al., 1994; Reimer et al., 2014; but see Megemont et al., 2022). Still however, surprisingly few studies have used pupillometry to further clarify the role of NE fluctuations in response inhibition.

So far, only two studies (i.e., Chatham et al., 2012; Schevernels et al., 2016) have explored the relationship between naturally-occurring NE and the dynamics of response inhibition in a combined stop-signal task-pupillometry setting. Both studies investigated the transient pupil response to the stop signal, as a marker of the phasic NE response, compared to go trials; and Schevernels et al. (2016)

additionally investigated the difference in transient pupil response to successful versus unsuccessful stop trials (particularly in the context of vagus-nerve stimulation in patients with epilepsy, which is also believed to affect NE levels). Transient pupil size was larger when stopping was needed (versus not needed, i.e., stop versus go trial) and unsuccessful (versus successful, and under vagus-nerve stimulation). However, while the transient pupil response may well be related to the (phasic) NE system, the transient pupil response in a stop-signal task is hard to interpret specifically on a mechanistic level because different trial types differ along various dimensions (e.g. the presentation of one vs. two imperative stimuli, the execution of a motor response versus not, the detection of an unsuccessful outcome, as well as varying speeds of the ongoing go responses and varying SSDs), many of which are likely reflected in the pupil response to the stop-signal task (Steinhauer et al., 2022).

Furthermore, the previous studies did not investigate any pretrial pupil measures, as a marker of fluctuating tonic NE levels. Arguably, it would be the tonic level at the moment of task presentation that (also) affects the dynamics of the response-inhibition race, as that would be more related to e.g. the earlier pharmacological work (which also tonically changes NE levels). Moreover, it appears particularly plausible for response inhibition that pretrial brain fluctuations affect its dynamics in a given trial. This is based on behavioral work showing that response inhibition is already (partly) proactively determined, i.e. before inhibition is even needed (see e.g., Bissett & Logan, 2011; Doekemeijer et al., 2023; Logan, 1981; Ramautar et al., 2004; Verbruggen & Logan, 2009) and on theories suggesting that there is a clear and separable role for proactive control particularly in inhibition on a stop-signal task (Kenemans, 2015; Wessel, 2018).

1.2 The current study

In the present study, we investigated the link between pretrial pupil measures and response inhibition in order to determine whether, and to which degree tonic NE levels play a role in the moment-to-moment behavioral fluctuations in response inhibition in the stop-signal task. We used two pretrial measures: the absolute pretrial pupil size and its rate of change right before the onset of the go stimulus (which indicates whether the pupil was dilating or constricting at that moment, usually called "pupil derivative"), as both measures have been linked to tonic NE levels. Furthermore, we looked at three main performance measures that can be obtained from the stop-signal task: stopping success (i.e., whether the stop response successfully won the race), the speed of the go response (Go reaction time, GoRT), and the speed of the stop response (SSRT). Based on previous work, we expected to find a link between the two pretrial pupil measures and any of the behavioral measures, and particularly that higher pretrial pupil measures go together with faster SSRTs.

To test these hypotheses, we ran two experiments: the first experiment (EXP1) consisted of a typical stop-signal task, whereas the second experiment (EXP2) consisted of the same stop-signal task, which

was interleaved on a block-level with an identical task, in which participants were instructed to ignore the stop signals completely (ignore task). EXP2 was run after the data analysis of EXP1; and it allowed us to not only replicate our findings of EXP1 but also to subsequently isolate the effect of the stopping context on the GoRT (i.e., to determine whether any effects of pretrial pupil measure on GoRT held up outside of the stopping context or whether they were stopping-context-specific), following behavioral work showing that people tend to specifically adjust (i.e., slow down) their GoRT in a stopping-context (Verbruggen & Logan, 2009). Thereby, using pretrial pupil measures, we were able to thoroughly investigate the link between naturally-occurring fluctuations in tonic NE levels and behavioral fluctuations in the race of response inhibition.

2 Methods

2.1 Ethics Statement

This research was conducted according to the ethical rules presented in the General Ethical Protocol of the Faculty of Psychology and Educational Sciences of Ghent University.

2.2 Participants

For EXP1, we recruited 31 first-year Bachelor Psychology students at Ghent university using the Sona Systems recruitment platform (Sona Systems, https://www.sona-systems.com/). This sample size is typical of recent related pupillometry work (e.g. Tromp et al., 2022; van den Brink et al., 2016) and allowed us to capture effects around d=0.5 given power=0.8 (Brysbaert, 2019). For their participation, participants earned one course credit each. All students were between 18-35 years old and had perfect vision or used lenses. The data was further checked for any other reasons for exclusion after data collection was completed (based on earlier work and guidelines, respectively Doekemeijer et al., 2021; Verbruggen et al., 2019): (1) the accuracy on go trials was lower than 90%; (2) the probability to respond to a stop signal, $p(R|S)$, was under 30% or over 70%; (3) the context-independence assumption was violated (as determined by the mean RT on unsuccessful stop trials - i.e., signal-respond RT, SRRT - being longer than the mean RT on go trials, GoRT); (4) participants had slowed down considerably over the course of the experiment (as determined as the mean GoRT in the last block being longer than 1.5 times the mean GoRT in the first block). We additionally checked for each participant if the GoRT distribution was truncated, which would indicate that late responses might not have been registered. None of the participants were excluded based on these criteria. Overall, our sample consisted of 25 female and 6 male participants, aged 22 years old on average (SD = 2.99).

For EXP2, we collected data of 26 participants (whereas for an additional three participants, part

of the data was either lost or the experiment was stopped early). Using the same exclusion criteria as above, we excluded three more participants due to them not following instructions properly (i.e., therefore bringing their go accuracy on trials in which signals had to be ignored below 90%). The final sample of 23 participants consisted of 15 women and 8 men, aged 24 (6.26) on average(allowing us to capture effects around d=0.6 given power=0.8; Brysbaert, 2019).

2.3 Materials

2.3.1 The stop-signal task

In this study, we used a typical stop-signal task (coded in OpenSesame (Mathôt et al., 2012) for EXP1 and in PsychoPy (Peirce, 2007) for EXP2) with a dark color scheme to minimize pupil-light reflexes (see figure 1 left). The code for both tasks can be found on OSF: https://osf.io/t8chy/. The stop-signal task of EXP1 consisted of 67% go trials and 33% stop trials; for EXP2, we changed this to 75% go trials and 25% stop trials, to follow the recommendations of Verbruggen et al., 2019 even more strictly.

The go trials in EXP1 consisted of an arrow which lasted for 600 ms (the go stimulus) followed by a fixation cross (inter-trial interval) which lasted variably between 1250 and 1450 ms; the last 250 ms of this interval were considered the baseline period of the next trial. All the stimuli were black (RGB = [0, 0, 0]) and appeared on a gray background (RGB = [128, 128, 128]). Participants were instructed to respond to the direction of the arrow (left or right) with the left and right keys on a standard keyboard using the index and middle finger of their preferred hand respectively.

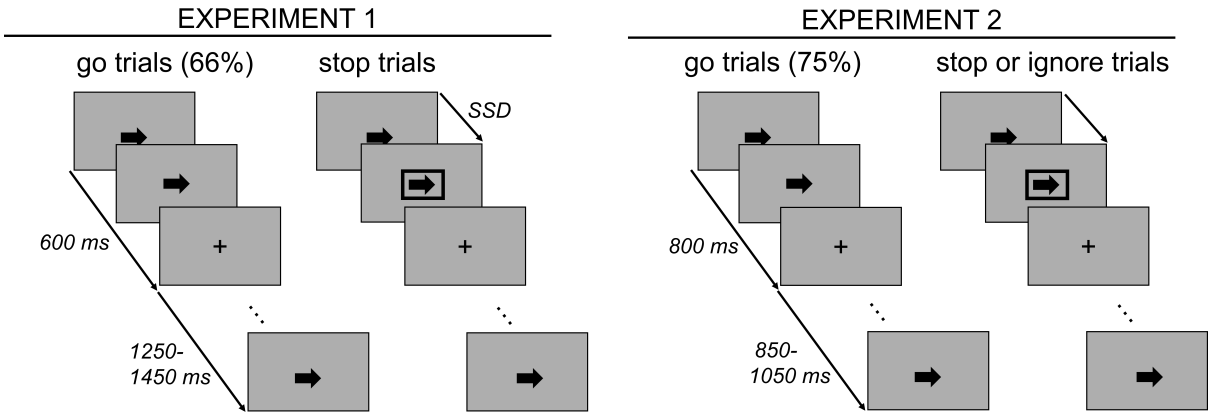

Figure 1: The stop-signal task used in EXP1 (left) and EXP2 (right).

On stop trials, an additional stop signal (black rectangle) appeared with some delay after the onset of the arrow (i.e., the SSD, ranging between 50 ms to 550 ms). In stop trials, participants had to withhold their response to the arrow if the stop signal appeared, but were instructed not to wait for the signal to appear. After each stop trial, the SSD was updated according to an adaptive staircase: if the stop trial

was successful, the signal was delayed by 34 ms (two frames at 60 Hz); if unsuccessful, it was shortened by 34 ms. This was done to ensure that the p(respond|signal) was approximately 50%, which is ideal for the estimation of the stop-signal reaction time (SSRT, see below). Furthermore, we used two randomly interleaved staircases to ensure the randomness of the trial sequence before successful and unsuccessful stop trials (as done before by e.g. Aron & Poldrack, 2006), which may otherwise be more likely to succeed each other (i.e., a successful stop trial would be more likely to be proceeded by an unsuccessful one, and vice versa, due to the adaptive SSD staircase adjusting the difficulty of the subsequent trial). This may be particularly problematic for pretrial pupil measures, which may still reflect the outcome of the previous trial; any non-randomness in trial sequences may therefore pose a threat concerning differential overlap.

From the behavioral data, we determined the participant's average reaction time on go trials (GoRT), accuracy on go trials (split between incorrect responses, called 'choice errors'; and non-responses, 'go omissions'; which will not be further analyzed here given that they happened too sparsely), whether each stop trial was successful or not (stopping success), and the average reaction time on failed stop trials (signal-respond reaction time, SRRT; which was solely used to check whether the context independence assumption of the horse-race model was violated).

For EXP2, we reran the above experiment with slightly different parameters (see figure 1 right). We interleaved the standard stop-signal task blocks with blocks in which participants were told to ignore the 'stop' signals altogether (on the so-called "ignore blocks"), making the experiment twice as long compared to EXP1. So, instead of inhibiting their response when a signal appeared, participants had to ignore that signal by still responding to the arrow on signal trials (i.e., "ignore trials"; as done before by Verbruggen & Logan, 2009). A stop block always preceded an ignore block, as all SSDs of the preceding stop block were reused for the ignore trials (although note that the trial sequence was still randomized). EXP2 allowed us to both replicate our results of EXP1 with slightly different task parameters, and to additionally investigate whether the link between pretrial pupil measures and GoRT was affected by context (i.e., by comparing performance in the stop blocks versus those on the ignore blocks).

2.3.2 Pupillometry

We used an EyeLink 1000 Plus desktop-mount eyetracker while participants were performing the stop-signal task in a dimly-lit room. The task was shown on a screen monitor (BenQ XL2420TE LCD) that had a resolution of 1920x1080 px and a refresh rate of 60 Hz. The eyetracker was placed in the center in between a chin rest and the screen monitor (i.e., 50 cm between both); the monitor was hence at a distance of 100 cm from the participants' eyes. The ambient lighting stayed consistent across participants. From the eyetracker, we obtained the absolute pupil size continuously from both eyes with a 500

Hz sampling rate.

2.4 Procedure

Upon arriving, participants were asked to remove any eye make-up they had on. When ready, participants were seated in front of the eyetracker and the head rest was adjusted to make sure the participant was positioned comfortably and in view of the eyetracker. Furthermore, at this time, the room light was dimmed so that the participants' pupils could already adapt to the brightness setting. Participants were asked to sign an informed consent, after which the eyetracker was calibrated using a nine-point calibration procedure. Subsequently, the participants were provided with the task instructions, which stressed the need for fast and accurate responding, to not to slow down strategically, and that non-responses on go trials (go omissions) had to strictly be avoided. Furthermore, the participants were instructed to keep fixating on the fixation cross throughout the experiment and to blink as little as possible during the experiment.

To familiarize participants with the go and stop trials, two practice blocks followed the instructions: one consisting of ten go trials and the next consisting of eight go and four stop trials. Participants received immediate feedback after each trial in these practice blocks. After practice, eight experimental blocks (consisting of 48 trials: 32 go trials interleaved with 16 stop trials) followed the practice blocks; no more trial-level feedback was provided in this experimental phase. Between blocks, participants received feedback about their performance both on-screen as well verbally from the experimenter to ensure that the participants understood (and followed) the instructions properly. At the end of each experimental block, the eyetracker was recalibrated if needed (i.e., if the one or both eyes were out of focus). Additionally, participants were instructed to rest their eyes for a while before starting the new block.

2.5 Preprocessing

All preprocessing was done using the Pypillometry package in Python (Mittner, 2020); the statistical analyses were subsequently conducted in R Statistics (version 4.2.2, R Core Team, 2021) using the rstatix package(version 0.7.2; Kassambara, 2021) and using the lme4 package to fit the models described below (version 1.1-35.1; Bates et al., 2015). The data, preprocessing and analyses scripts, and supplementary materials can be found on OSF: https://osf.io/t8chy/. In the supplementary materials, we additionally briefly review the relationship between transient pupil size (i.e., the pupil response after the go stimulus), pretrial pupil size, and response inhibition in our data.

We first investigated the behavioural data according to guidelines set by Verbruggen et al. (2019).

Specifically, we determined each participant's average GoRT and the percentage of choice errors and go omissions on go trials; and their average SRRT, SSD and $p(R|S)$ on stop trials. We subsequently estimated the stop-signal reaction time (SSRT) using the integration approach with replacement of go omissions follow standard guidelines by Verbruggen et al. (2019); in this method, the mean SSRT is estimated as the outcome when the mean SSD on stop trials is subtracted from the n^{th} RT on go trials, sorted from small to large; in which n is the $p(R|S)$ and go omissions are assigned large values (here, 1000 ms) and thus appear at the end of the sorted RT array. Finally, we removed all choice errors from our data (due to the sparsity, we could not analyze the pupil data of the incorrect trials properly), and the GoRTs were log-transformed (to make them normally distributed) and z-scored within blocks (to account for the tendency for the GoRT to slowly increase throughout a block, and following Tromp et al., 2022; van den Brink et al., 2016). For EXP2, we additionally checked the accuracy on ignore blocks; blocks with an accuracy of 90% or below were removed resulting in a total of 16 (out of 230) blocks to be removed.

The pupil data of both eyes were averaged; if there was data available for only one eye, those values were used instead. Second, we detected the blinks within the pupil data (as values were the pupil size was zero), merged subsequent blinks if they occurred within 100 ms of each other, and finally interpolated them following the method of Mathôt (2013). For our analyses, we considered the 250-ms pretrial time window before go-stimulus onset (i.e., [-250 ms, 0 ms]). From this window, we extracted two pretrial pupil measures: (1) the absolute pupil size (PS), which was z-scored per task block; and (2) the derivative of the pupil size (dPS) as computed as the change between the average pupil size in the time window [-100 ms, -50 ms] and [-50 ms, 0 ms]), then log-transformed and z-scored per task block again.

As a last step before the statistical analyses, we removed the practice trials and the first trial of each block from both the behavioral and pupil data.

2.6 Statistical analyses

For EXP1, we conducted six analyses to establish the relationship between pretrial pupil measures (PS, dPS) and response inhibition (stopping success, GoRT, and SSRT). To establish whether pretrial pupil size predicted the success of a stop trial (successful vs unsuccessful), we conducted two generalized logistic models. More specifically, we used models to predict the odds of a stop trial being successful (vs unsuccessful) using the pupil measure (i.e., pupil size, PS; or pupil derivative, dPS) as a regressor and a random-intercept for each participant, while accounting for a range of variables that might confound our results (i.e., the current trial's SSD and trial number; and the previous trial's peak amplitude, intertrial interval, and whether there had been a manual response or not). To predict GoRT using the pretrial pupil measures, we used two generalized linear models, which predicted the z-scored, log-transformed

GoRT from the pupil measure (PS or dPS) and included a random-intercept for each participant and the same control variables as before (minus the SSD). For SSRT, we could not use a regression model to investigate its relationship with the pretrial pupil measures, since SSRT estimates can only be obtained for (at most, a subsection of) a whole data set; therefore, we split the data into two groups based on average pretrial pupil measure (resulting in two data subsets containing relatively small versus large PS or dPS; this split was done separately for both stop trials and go trials to obtain matching go trials for the SSRT estimation), and estimated the SSRT for each subset of the data. We then performed (two-sided) paired t-tests to establish whether the difference in SSRT between small versus large PS and between small versus large dPS were significantly larger or smaller than 0.

For EXP2, we followed the same statistical analysis plan, and additionally investigated whether the predictive nature of PS and dPS on GoRT was modulated by context. In other words, we additionally investigated the two interaction terms between pretrial pupil measures and context (stop blocks versus ignore blocks), so that the models predicted the z-scored, log-transformed GoRT from the pupil measure (PS or dPS) for each context (stop vs ignore) and a random-intercept for each participant.

3 Results

3.1 Performance and pupil data quality

3.1.1 Behavioral overview

An overview of the behavioural data for both EXP1 and EXP2 (split between stop and ignore blocks) is provided in Table 1. For EXP1 and the stop blocks of EXP2, the results are in line with what is typically observed in stop-signal tasks: there were few choice errors and go omissions, and mean GoRT was fast and consistently longer than SRRT (in line with predictions of the independent race model). Moreover, the $p(R|S)$ was approximately 50% as expected from the adaptive staircase procedure. Finally, the SSRT was in the typical range of around 200 ms. We additionally checked the important assumption that the double adaptive staircase was also successful in establishing a random trial sequence, including the factor of stopping success (see the supplementary materials on OSF for more details). Overall, the behavioral results in EXP1 and that on the stop blocks of EXP2 was very similar. For EXP2 we additionally observed that responding on go trials was slower on stop blocks compared to ignore blocks, representing the typical proactive slowing that tends to occur when stopping is involved; and that responding tended to be a bit slower on ignore trials compared to go trials (numerically; Verbruggen & Logan, 2009).

3.1.2 Pupil data quality

For the pupil data, we investigated the general overlap in pretrial pupil measures between go and stop trials (see figure 2) as data quality measure. Specifically, we looked at this comparison because, at that

Table 1: Means and standard deviations (in brackets) of the behavioral data of EXP1 and EXP2, in which we added blocks where participants had to ignore the stop signal ("ignore" blocks).

	EXP1 (N=31)	EXP2 (N=23)	
	Stop blocks	Stop blocks	Ignore blocks
Go trials			
GoRT (ms)	442 (44)	438 (50)	377 (26)
Choice errors (%)	1.3 (2.6)	1.3 (2.2)	3.0 (2.1)
Go omissions (%)	0.7 (1.2)	0.3 (0.6)	0.2 (0.3)
Stop and ignore trials			
SSD (ms)	227 (52)	218 (66)	-
p(Respond|Signal)	51.2 (2.6)	50.4 (3.5)	97.5 (1.9)
SRRT (ms)	399 (35)	396 (33)	386 (32)
SSRT (ms)	202 (31)	202 (36)	-

GoRT = reaction time on go trials; SSD = stop-signal delay; SRRT = signal-response reaction time (i.e., in EXP2, on stop trials in stop blocks and on ignore trials in ignore blocks); SSRT = stop-signal reaction time.

moment, participants could not know whether a go or a stop trial is about to occur; as such there should be no difference in pretrial pupil size between those trial types. As expected, for EXP1, a linear model with PS as dependent variable, trial type (go versus stop trial) as independent variable and a random effect for participant clearly indicated that go and stop trials were similar during the pretrial period, F (1, 30) = 0.01, p = .91. There were also no differences between go and stop trials for dPS, F (1, 30) = 0.44, p = 0.51.

Similarly to EXP1, we did not observe any pretrial differences between go and stop trials (on stop blocks for EXP2) with respect to PS, F (1, 22) = 0.03, p= .87, but a trend-level difference for dPS, F (1, 22) = 3.89, p = 0.06. In the ignore blocks, we found an unexpected difference between go trials and ignore trials for PS, F (1, 22) = 9.65, p = 0.005, but not for dPS, F (1, 22) = 0.02, p = 0.88. Although these results do not indicate a perfectly balanced set-up preceding every trial type across both measures in EXP2, it is important to note that pupillometry is very sensitive for small differences, and can easily pick up e.g. very subtle differences in trial history (which was slightly less perfectly balanced in EXP2, see supplementary materials on OSF). Yet, it is important to note that our main analyses focus on variation within trial types, and to relate it to performance on that trial, rather than trial type.

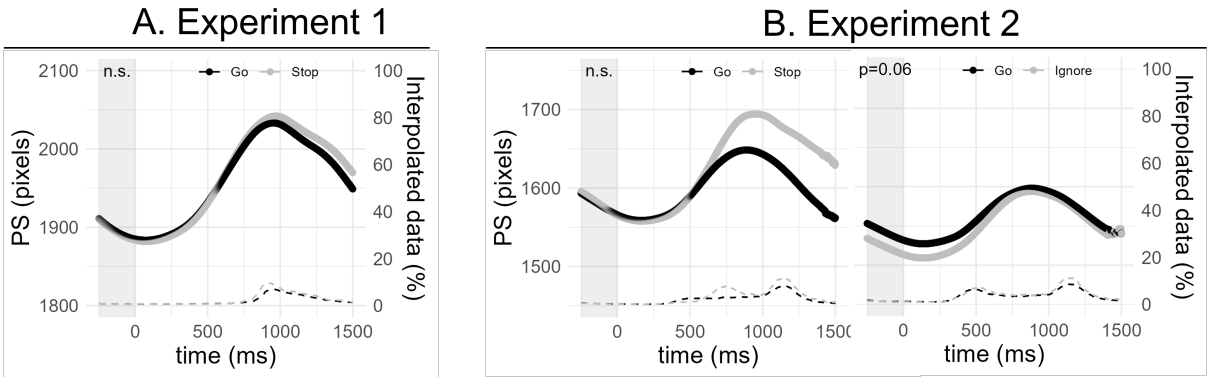

Figure 2: The average, non-baseline-corrected pupil size before and throughout a trial, which should not differ in the pretrial period, in (A) EXP1, a go trial (black solid line) versus a stop trial (grey solid line); (B) EXP2, (left) a go trial versus a stop trial on stop blocks and (right) a go trial versus a ignore trial (grey) on ignore blocks. The pretrial period is the time before the onset of the go stimulus and is indicated in light grey. On the secondary y-axis, the percentage of interpolated data is provided for each time point and condition (dashed lines), note that very few data points were interpolated in the pretrial period which we investigated in our study.

3.2 Pupil analyses

A visual overview of the results of both EXP1 and EXP2 is provided in figure 3. We go over each result in more detail below. Analyses on the transient pupil response are listed in the supplementary materials, as well as the full results of each model (i.e., including the results on the confounding factors).

3.2.1 Pretrial pupil size predicting stopping success

We conducted two generalized logistic models to establish whether PS and/or dPS predicted the success of a stop trial (successful versus unsuccessful) in EXP1, while accounting for potential confounding factors (the current trial's SSD and trial number; and the previous trial's peak amplitude, intertrial interval, and whether there had been a manual response or not). The first logistic model showed that PS did not predict stopping success, $Log - Odds$ = -0.05 (95%-confidence interval: [-0.12, 0.02]), z = -1.32, p = 0.187; the second logistic model revealed that dPS did predict stopping success, $Log - Odds$ = -0.11 [-0.16, -0.05], z = -3.48, p = 0.001. Particularly, a higher dPS predicted a lower stopping success. In EXP2, we replicated these findings for dPS, $Log - Odds$ = -0.11 [-0.19, -0.02], z = -2.48, p = 0.01, and for PS, $Log - Odds$ = 0.04 [-0.05, 0.13], z = 0.83, p = 0.41 (but note that even the numerical trend is swapped, emphasizing the lack of consistency between the two experiments). Given that stopping success is driven by both the in-the-moment GoRT and SSRT, this finding is difficult to understand alone. Therefore, next we analyzed the link between pretrial pupil measures on GoRT and SSRT to gain more insights into the dynamics of the response-inhibition race, of which stopping success is just the outcome.

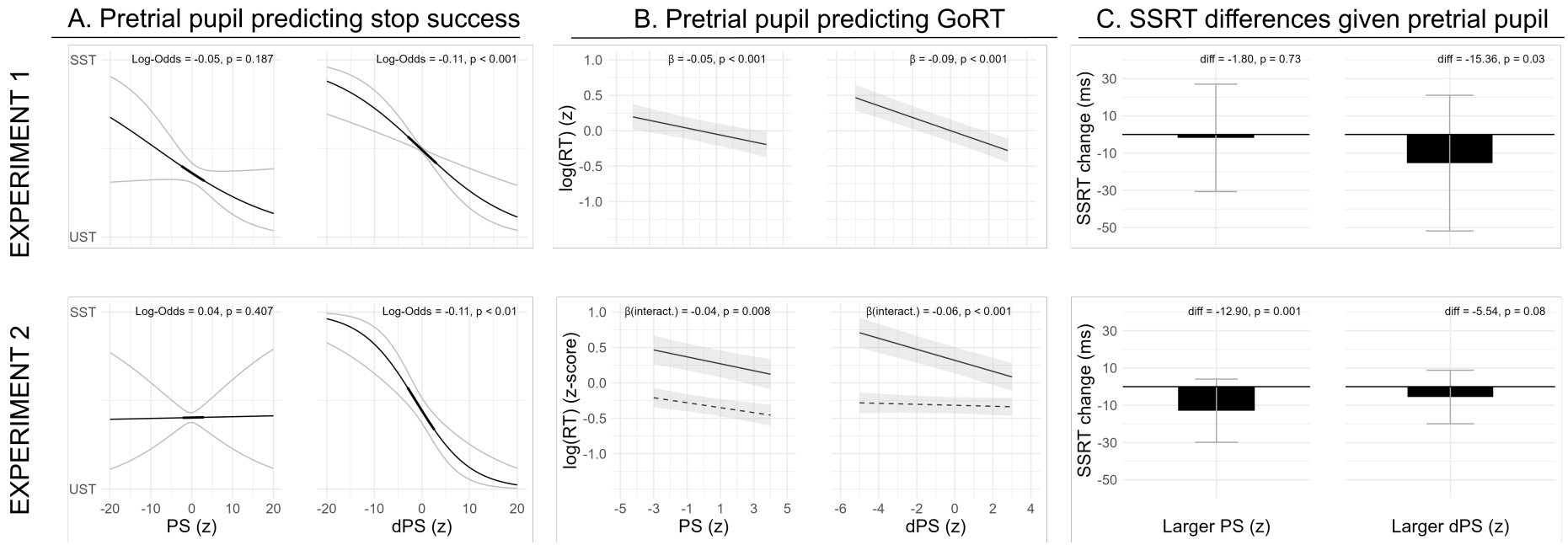

Figure 3: Results overview showing the role of pretrial pupil measures (absolute pupil size, PS, and its derivative, dPS) on response inhibition performance (stopping success, left; GoRT, middle; and SSRT, right) for EXP1 (top row) and EXP2 (bottom row). For EXP2, we also investigated GoRT in ignore blocks (plotted as the dashed line). The panel on the right shows the effects of pupil size and its derivative on SSRT as the difference from zero for larger PS and dPS, with negative values indicating a shorter SSRT for these conditions.

3.2.2 Pretrial pupil size predicting GoRT

We set up generalized linear models[2] that predicted GoRT from PS or dPS while accounting for the potential confounding factors (the current trial's trial number, and the previous trial's peak amplitude, intertrial interval, and whether there had been a manual response or not). For EXP1, the first model showed that PS significantly predicted GoRT, with larger PS predicting shorter GoRTs, β = -0.05 [-0.07, -0.02], t = -3.98, $p < 0.001$. The second model showed that larger dPS also predicted shorter GoRTs, β = -0.09 [-0.11, -0.08], t = -10.06, $p < 0.001$. This pattern is in line with earlier work from other task domains showing that higher PS (e.g., van den Brink et al., 2016) and dPS (e.g., Tromp et al., 2022; van den Brink et al., 2016) relate to faster responses in other cognitive-control tasks.

For EXP2, we extended the initial two generalized linear models to have an interaction effect between pretrial pupil size (PS or dPS) and block context (stop versus ignore), in order to investigate whether the context modulated the initial main effect of PS and dPS on GoRT. We found significant interaction effects in both models, indicating that both the effect of PS and dPS on GoRT depended on context, PS: β = -0.04 [-0.07, -0.001], t = -2.64, p = 0.008; dPS = β = -0.06 [-0.09, -0.03], t = -4.26, $p < 0.001$. The effect was stronger in stop blocks than in ignore blocks for both PS and dPS; in fact, for dPS we found that the effect was *only* present for stop blocks (as revealed by post-hoc models), stop blocks: β = -0.08 [-0.10, -0.06], t = -7.50, $p < 0.001$; ignore blocks: β = -0.0006 [-0.03, 0.01], t = -0.74, p = 0.46; though it was present for both stop and ignore blocks for PS, stop blocks: β = -0.05 [-0.07, -0.02], t = -3.96, $p < 0.001$; ignore blocks: β = -0.04 [-0.06, -0.01], t = -3.05, p = 0.002. This indicates that dPS predicts GoRT but only in a general stopping context (or, at least, a somewhat cognitively-demanding task).

3.2.3 Pretrial pupil size and SSRT

Using a paired t-test, we found that the SSRTs did not differ between large versus small PS for EXP1, t (30) = -0.3, p = 0.73; yet, that they were significantly shorter for larger dPS, t (30) = -2.3, p = 0.03. In EXP2, this relationship was observed in a way that was switched between the two pupil measures: shorter SSRT were observed for larger PS, t (22) = -3.6, p = 0.001, but not for dPS, for which, however, there was a statistical trend in the same direction, t (22) = -1.8, p = 0.08.

[2]We additionally checked whether a quadratic model would fit the data better, given that it has been reported that reaction times and pretrial pupil size are related in an inverted u-shape (Beerendonk et al., 2024). However we did not find any conclusive evidence that the quadratic model fit our GoRT data better than our linear model based on the AICs. We found similar inconclusive results for stopping success and SSRT; see the supplementary materials for more details on these polynomial analyses.

4 Discussion

In this study, we conducted two experiments to investigate whether and in which ways pretrial pupil measures, which are believed to be indicative of tonic NE levels in the brain, relate to behavioral fluctuations in response inhibition. We found that both pretrial pupil measures generally predicted stopping success (except for absolute pupil size in EXP2) and GoRT: a larger pretrial pupil derivative predicted faster GoRT and less successful stopping. We additionally showed in EXP2 that this effect on GoRT was partly driven by the stopping context, since the effect was weaker in task blocks in which participants never had to inhibit their response. For the SSRT, we observed slightly less consistent effects across our experiments: we found that a larger pupil derivative was associated with a shorter SSRT in EXP1, but this was only at trend-level in EXP2; conversely, we only found a larger absolute pupil size to have such an effect on SSRT in EXP2, but not in EXP1. These links between pretrial pupil measures and response inhibition ultimately suggest that moment-to-moment behavioral fluctuations are regulated by fluctuations in tonic NE levels, and that this is specifically done by regulating both the speed of the go response and, to some extent, also that of the stop response.

4.1 The influence of pretrial states on the speed of the go response

Among the three main behavioral parameters we looked at, the relationship between pretrial pupil measures and GoRT is likely the most straightforward to interpret, and the effect that is most directly related to earlier findings. Specifically, our results are in line with previous pupillometry research showing that people respond faster on cognitive tasks when pretrial pupil measures are larger (e.g., Tromp et al., 2022; van den Brink et al., 2016); we add here that this also true for the stop-signal task. This dovetails with the behavioral findings showing that the GoRT in the stop-signal task is significantly modulated proactively, with the general tendency of participants to always want to actively delay their responses in anticipation of needing to stop (Bissett & Logan, 2011; Doekemeijer et al., 2023; Logan, 1981; Ramautar et al., 2004; Verbruggen & Logan, 2009). Further to this point, we found in EXP2 that pretrial pupil measures most strongly predict GoRT when stopping is involved, so when proactive slowing is most pronounced. Correspondingly, our results suggest that the degree of proactive slowing GoRT may be related to tonic NE levels in the brain, as captured by the pretrial pupil size.

However, the direction of such a relationship suggests that higher levels of NE downregulate the degree of proactive slowing of the GoRT, as higher pupil measures predict faster GoRTs, so less proactive adjustments. This ultimately implies a rather straightforward relationship between NE and GoRT in that people are simply more ready to react when tonic NE levels are relatively high. The effect is amplified when stopping is involved, even though this is not to the benefit of stopping itself as people are less likely to successfully stop with faster GoRTs (i.e. according to the horse-race model). In this sense,

our results on particularly the pupil derivative is in line with e.g. Tromp et al. (2022), who found that reaction times to incongruent Stroop stimuli were also faster when the pupil derivative was high even though this is not necessarily beneficial to the overall task at hand. Furthermore, it is in line with animal work showing that a larger pupil size and pupil derivative simply speed up responding to task-relevant stimuli (in line with the idea by Reimer et al., 2016, that larger pupil derivative is related to enhanced visual encoding), irrespective of whether these signals trigger a go or a stop response; and, as seems clear from our findings on stopping success, that this is not always to the benefit of the accuracy of the (response-inhibition) outcome itself. In our study, we did not further investigate accuracy on go trials (given that participants made very few errors), but more work can investigate the effect of NE on go accuracy; in line with the increased visual encoding process, it should be expected that not only GoRT (as we see here) is improved but also go accuracy.

4.2 The influence of pretrial states on stopping success and the speed of the stop response

Following the horse-race model and the fact that GoRT is sped up with higher tonic NE levels, it is a perhaps a logical consequence that we found that pretrial pupil measures also predicted stopping success, i.e. higher pretrial pupil derivative was linked to less stopping success. This very likely reflects the fact that faster speed of the go response makes the race hard to be won by the stop response if the stop response is not regulated in a similar, if not stronger, way as the go response; this is particularly true since the GoRT is typically much longer than the SSRT, so if both responses are sped up with the same rate, the GoRT will be sped up more than the SSRT. Concerning the latter, we did find some evidence of such a modulation of tonic NE levels on the speed of the stop response, although not fully consistently across all tests: the SSRT tended to be faster when pretrial pupil size or its derivative were large. In general, this is in line with previous work linking (increased) tonic NE levels to (shorter) SSRT in particular (Robbins & Arnsten, 2009; Tomassini et al., 2022). However, based on the stopping-success findings, such a modulation on the SSRT was apparently not sufficient to also manifest itself in improved stopping success.

One limitation with respect to our investigation on the SSRT is that we had to infer a single SSRT estimate from (at best, a big subset of) our data, since the SSRT cannot be directly observed in classic stop-signal tasks. Therefore, our SSRT analyses may be less sensitive than the single-trial based analyses we did here for GoRT and stopping success. Future research could address this issue by using mouse-tracking in continuous stop-signal tasks (e.g., Hannah et al., 2022; Morein-Zamir & Meiran, 2003; Schultz et al., 2023), which allows trial-by-trial measures of stopping latency. Such a continuous task would therefore make analyses more sensitive to capture pupil effects on SSRTs (yet, would also make it more difficult to not have people moving their eyes).

4.3 The role of pretrial states on response inhibition do not appear stopping-specific

Altogether, our work provides evidence that there is a link between naturally-occurring tonic NE levels and all central behavioral aspects of response inhibition, meaning that tonic NE might play a pivotal role in understanding moment-to-moment behavioral fluctuations in response inhibition. It furthermore suggests that this role of NE is rather general, as tonic NE appears to be involved with both the stop response as well as the go response. Overall, this is against earlier work suggesting that the effect of the NE system is stopping-specific (e.g., Robbins & Arnsten, 2009).

That said, in so far as it is trying to relate our findings to earlier NE-related pharmacological intervention studies on response inhibition, our work is based on the idea that the pretrial pupil measures indeed reflect tonic NE levels (following Gilzenrat et al., 2010; Rajkowski et al., 1994; Reimer et al., 2014). Yet, this idea has also been outright contested (e.g., Megemont et al., 2022), and there is also a growing body of work showing that pupil size reflects more than the activity of the NE system (Cazettes et al., 2021; Reimer et al., 2016). Specifically, pupil size has been demonstrated to reflect activity of a large arousal network that involves, besides the NE system, also the cholinergic system, dopamine system, and the serotonin system (De Gee et al., 2017; Joshi et al., 2016; Lloyd et al., 2023); as such, pupil size is influenced by multiple neuromodulatory systems, and LC/NE-independent contributions of other systems have been directly demonstrated. In an animal study, Reimer et al. (2016) provided evidence more specifically that some pretrial pupil measures may be more linked to the cholinergic system rather than the NE system; they suggested that pupil derivative is likely more reflective of NE levels, whereas absolute pupil size may be more related to the cholinergic system. A further investigation on (the interactions between) the cholinergic system, the NE system, and other modulatory systems of the larger arousal network (such as the dopaminergic and serotonergic ones) may therefore be interesting. Dissociating their individual and combined roles would be useful concerning the behavioral fluctuations of response inhibition (see Liu et al. (2024) for such a recent study in mice), as well as in a broader concept of arousal. Presumably, at a process level, the neuromodulatory systems contribute to arousal in an overlapping fashion; while a further distinction of the contribution of various neuromodulatory systems may hold additional explanatory power, conceptually, if arousal is what drives our moment-to-moment differences in response inhibition, such differentiation between the various systems might ultimately not be essential. Still, ultimately, this would mean that the role of NE in response inhibition is neither stopping-specific nor unique.

4.4 Conclusion

In our study, we consistently established that pretrial pupil measures predicted response-inhibition behavior. This was the clearest for GoRT in that people were faster when pretrial pupil measures were large, with the relationship especially pronounced in a stopping context. We argue that this effect also drives a lower stopping success in such a way that stopping success itself is also linked to larger pretrial pupil measures (albeit less consistently) via a faster go response, which makes responding more likely also on stop trials. With respect to the SSRT, we also found some evidence for a relationship between pretrial pupil measures (again, people were faster to stop when pretrial pupils were large), but this was also less consistent; although the overall trend of the relationship is in line with our expectation, we believe more work is needed to conclusively determine whether and to which degree there is a link between pretrial pupil measures and SSRT (e.g. using a continuous stop task). These results from pretrial pupil measures ultimately indicate that tonic levels of NE, are regulating the race of response inhibition, in ways that are set already at a pretrial stage. Given the fact that we found evidence that both GoRT as well as the SSRT were regulated this way, it appears that this role of tonic NE is not stopping-specific.

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